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Anticancer Activity of Organometallic Compounds. 3. The Reaction of Dimethyltin Dichloride with Nucleosides under Biologically Relevant Conditions

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Abstract

This paper reports the reaction of $SnMe_2Cl_2$ with adenosine, guanosine and inosine in aqueous solution at pH 4.5. The nucleosides give probably polymeric species in which there is monodentate coordination to O_2' of the ribose ring as indicated by 80 MHz PMR.

Introduction

The discovery that some organotin compounds have antitumour activity has aroused interest in the study of organotin compounds with nucleic acid bases [1, 4], nucleosides [1, 5–7] and carbohydrates [8]. Various bonding modes have been proposed (none yet confirmed by X-ray diffraction), (i) coordination of purine anions [4], unlikely in biological conditions, (ii) coordination of neutral purine bases through N_7 in free purines and nucleosides [1] and (iii) binding through deprotonated hydroxyl groups of the sugar ribose ring [5–8]. These various bonding modes are illustrated in Fig. 1.

A knowledge of tin-nucleoside binding is fundamental to an assessment of the anticancer properties of organotin compounds. If it is assumed they function through direct coordination to DNA, by analogy with the platinum group of drugs [9–12] which the organotins were originally designed to emulate, then there must be a preferred binding site on DNA which can be tentatively identified by suitable studies of model systems. Results which have relevance to biological systems can best be obtained by using reaction conditions of warm neutral aqueous solution. The aqueous chemistry of organotin halides is generally not well understood and is certainly complex though $[SnMe_2Cl_2]$ has been comparatively thoroughly studied [13] and is known to form the aqueous cation $[SnMe_2(OH)]^+$ in aqueous solution below about pH 5.

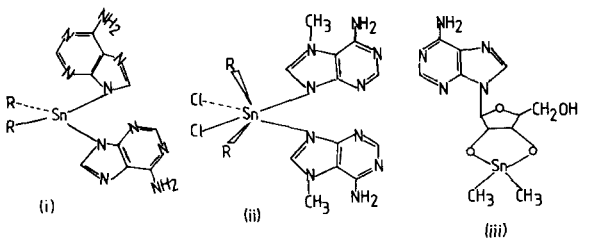

Fig. 1. Probable structure for the known organotin nucleoside purine base complexes.

Our approach to a model system for a possible R_2Sn^{II}–DNA interaction has therefore been to study the interaction of $[SnMe_2(OH)]^+$ with a series of nucleic acid components in aqueous solutions at pH 4–5. In this paper we report results with the nucleosides guanosine, adenosine and inosine. Compounds of stoichiometry $[SnMe_2(nucleoside)]$ have been previously isolated from refluxing anhydrous methanol [6, 7], though never crystallized for X-ray diffraction, and we felt it was of great interest to study the corresponding reaction under biologically relevant conditions.

Results and Discussion

The investigation of the reactions of organotin compounds in aqueous media is limited due to their low solubility and in some cases, hydrolytic instability. However, it is known that the water soluble $[SnMe_2Cl_2]$ produces dimethyltin(IV) ions on dissolution and at pH range $1 < pH < 8$, the species $[(CH_3)_2SnOH]^+$ and the dimer $[\{(CH_3)_2SnOH\}_2^{2+}]$ predominate [13]. Hence the reactions carried out between pH 4–5 in this study are essentially the reactions of these tin species with the nucleosides, and so may be very relevant to the functioning of organotin anticancer compounds.

The analytical, IR and NMR data for the new compounds are presented in Table I–III.

The compounds are formed as water insoluble amorphous powders and are sparingly soluble in DMSO, being insoluble in the other common organic solvents. They have no sharp melting points, instead

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TABLE I. Analytical Data for the New Compounds[a] (% Found (calc.))

Compound	Melting point (°C)	C	H	N	Sn
$[Me_2Sn(O)Ado \cdot H_2O]_n$	230–254d	33.12 (32.09)	4.33 (4.45)	16.01 (15.60)	25.83 (26.45)
$[Me_2Sn(O)Guo \cdot H_2O]_n$	[b]	31.68 (30.98)	3.91 (4.30)	15.82 (15.06)	25.17 (25.54)
$[Me_2Sn(O)Ino \cdot H_2O]_n$	298d	32.59 (32.02)	4.43 (4.22)	12.63 (12.45)	25.87 (26.39)

[a]C, H, N were analysed by the Microanalytical Laboratory, U.C.D. Dublin, Sn was estimated gravimetrically as SnO_2. HAdo = adenosine, HGuo = guanosine, HIno = Inosine. [b]No decomposition up to 300 °C.

TABLE II. Relevant Infrared Absorptions[a, b]

Compound	$\nu(NH_2)$, $\nu(OH)$	$\nu(C{=}O)$	$\nu(C-O)$ in ribose/$\nu(C-O-Sn)$[c]	$\nu(Sn-C)$	$\nu(Sn-O-Sn)$
$[Me_2Sn(O)Ado \cdot H_2O]_n$	3360sb, 3190sb		1110s, 1088ssh, 1048m, 1035w	570m, 515w	452w, 430m
$[Me_2Sn(O)Guo \cdot H_2O]_n$	3360sb, 3235sb, 3185sb	1720sh, 1700s	1104s, 1084s, 1044m	565m, 510m	450m
$[Me_2Sn(O)Ino \cdot H_2O]_n$	3440sb	1720m	1122m, 1108m, 1082s, 1038m, 1020w	568m, 515w	448m
Adenosine[d]	3330sb, 3160sb		1142s, 1124s, 1107s, 1090m, 1070s, 1052s, 1010m		
Guanosine[d]	3454sb, 3304sb, 3194sb, 3124sb	1728m, 1686s	1124s, 1080s, 1044m		
Inosine[d]	3540s, 3379sh, 3310m, 3140m	1700s, 1695s	1132s, 1118m, 1082s, 1048m		

[a]All spectra were recorded on the Perkin-Elmer 599 as KBr pellets in the range 4000–600 cm^{-1}, and as Nujol mulls on CsI windows in the range 600–200 cm^{-1}. [b]Assignments are made according to ref. 25. [c]Absorptions between 1150–1000 cm^{-1} are considered. [d]Data included for comparison. s = strong, m = medium, w = weak, sh = shoulder, b = broad.

TABLE III. ^1H NMR Data for the Compounds[a, d]

Compound	$\delta(H_8)$	$\delta(H_2)$	$\delta(H_2O)$	$\delta(NH_2)$	$\delta(H'_1)$	$\delta(SnMe_2)$	$^2J(^{117,119}Sn-^1H)$[b] (Hz)
$[Me_2Sn(O)Ado \cdot H_2O]_n$	8.316	8.109	3.262	7.172	5.667 5.628	0.458	76.411
$[Me_2Sn(O)Guo \cdot H_2O]_n$	7.877		3.259	6.323	5.496 5.438	0.440	77.391
$[Me_2Sn(O)Ino \cdot H_2O]_n$	8.286	8.038	3.311		5.667 5.631	0.446	75.244
Adenosine[c]	8.350	8.157		7.306	5.933 5.856		
Guanosine[c]	7.922			6.421	5.734 5.658		
Inosine[c]	8.311	8.051			5.905 5.841		

[a]Spectra recorded by Bruker WP 80 (FT) NMR in saturated solutions of d^6-DMSO using internal TMS references. All shifts are in ppm downfield from TMS. Satisfactory integration of all spectra obtained. [b] $^{117,119}Sn$ satellites were unresolved and $^2J(^{117,119}Sn-^1H)$ refers to the average value. [c]Data included for comparison. [d]Assignments are made following refs. 22–24.

they decompose at high temperatures (Table I). These imply the compounds are polymeric in nature [14]. In addition the presence of $\nu(Sn-O-Sn)$ absorptions in the solid state at 450–430 cm^{-1} [6, 7, 15–17] is indicative of the polymeric character of the compounds. The $\nu(Sn-C_2)$ frequencies can be

identified around 570 (ν_{asym}) and 515 cm^{-1} (ν_{sym}) as medium to weak bands, and are consistent with the *cis*-disposition of methyl groups [6, 7]. The δ(C–O) modes of the alcoholic functions of the ribofuranose residues in the nucleosides appear in the regions 1200–1000 cm^{-1} [18]. In the pure nucleosides, this region is characterised by the presence of a number of strong to medium bands. Therefore, the ν(C–O–Sn) absorptions in the complexes which are expected to appear in the same region [6, 7, 15, 16] are difficult to assign with reasonable certainty. In the guanosine complex (between 1150–1000 cm^{-1}) the band at 1104 cm^{-1} may be attributed to ν(C–O–Sn), other bands in this region coincide clearly with the free nucleoside. In the adenosine complex, four new bands are observed replacing seven that are present in the free adenosine. Whereas in the inosine complex shifts occur in three bands with respect to the pure ligand and the appearance of a new band (at 1020 cm^{-1}) is observed.

The $\nu(NH_2)$, $\delta(NH_2)$ and ν(C=O) of the respective nucleosides are very slightly affected and so coordination through NH_2 or CO is unlikely. Slight shifts of these vibrations in their complexes may be due to the presence of different degrees of hydrogen bonding in the solid state.

The changes in the ν(OH) frequency clearly indicate hydroxyl group involvement in complex formation. Some of the sharp absorption attributable to the ν(OH) in the nucleosides are replaced by strong bands in the 4000–3185 cm^{-1} region which may also indicate the presence of hydrogen-bonded water molecule in the compounds [21].

All the complexes were examined by 80 MHz ^1H NMR in d^6-DMSO solution. They were insufficiently soluble in other solvents, including D_2O, and overnight accumulation of data (~14 h) was necessary even for a saturated DMSO solution. Bonding to the ribose ring is evident from the upfield shift in the ribose protons in contrast to a complete absence of effect on the purine ring proton shifts (Table III).

Monodentate binding of the Sn to O_2' of the ribose ring is indicated by the disappearance of the $-O_2'-H$ resonance but not the $-O_3'-H$ or $-O_5'-H$ resonances (Fig. 2), and further confirmed by the large upfield shift in the H_1' resonance in the complexes. The shift in the $-NH_2$ resonance is presumably due to a change in the extent of hydrogen bonding.

The Mössbauer spectrum of the adenosine complex [19] gives the value for nuclear quadrupole splitting, ΔE (mm s^{-1}) = 3.13 and isomer shift, δ (mm s^{-1}) = 1.13 which are consistent with a trigonal bipyramidal environment around the tin atom [see, e.g., 6, 7]. Thus on the basis of the above discussion we suggest that these complexes are polymeric with Sn–O–Sn bridges and *cis*-disposition

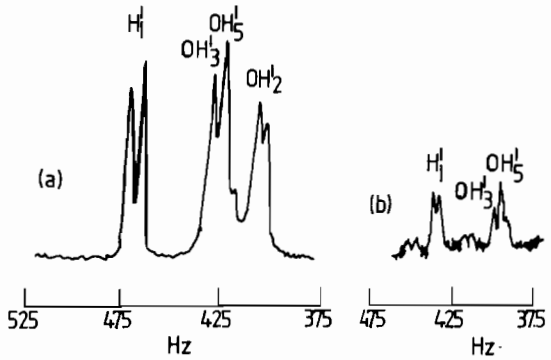

Fig. 2. ^1H NMR spectra of (a) adenosine and (b) $[Me_2Sn(O)Ado \cdot H_2O]_n$ in d^6-DMSO, at 80 MHz.

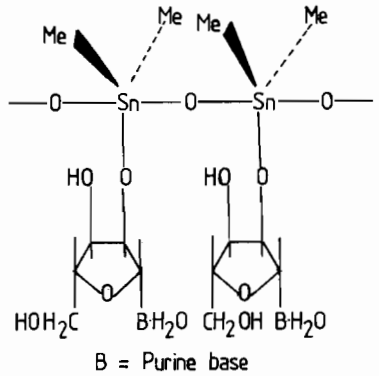

Fig. 3. Proposed structure for the new organotin nucleoside complexes.

of the methyl groups which produces a trigonal bipyramidal geometry around the tin atom (Fig. 3).

The new compounds resemble the previously reported [6, 7] monomeric or dimeric R_2SnL (R = Me, L = adenosine, guanosine, inosine) complexes in which the ligands are suggested to bind to tin through both $-O_2'$ and $-O_3'$. In our case the Sn–O–Sn linkages may have formed as a consequence of the following reaction sequence:

$$n Me_2SnCl_2 + n H_2O \rightleftharpoons n[Me_2Sn(OH)]^+ + n HCl + n Cl^-$$

$$n[Me_2Sn(OH)]^+ + n HNu \rightleftharpoons n[Me_2SnNu]^+ + n H_2O$$

$$n[Me_2SnNu]^+ + n H_2O \rightleftharpoons n[Me_2Sn(OH)Nu] + n H^+$$

$$n[Me_2Sn(OH)Nu] \rightleftharpoons \frac{1}{2}[\{Me_2Sn(O)Nu\}n] + \frac{n}{2}H_2O$$

The overall reaction, therefore, is

$$n Me_2SnCl_2 + n HNu + \frac{n}{2}H_2O \rightleftharpoons [Me_2Sn(O)Nu]_n + 2n HCl$$

where HNu = nucleoside

In view of the hydrolytic instability of the Sn–OC bonds in the simple alkoxides [20], the formation of the stable Sn–O–C linkage through ribose may be surprising but not unusual [8]. However, the hydrolytic stability of SnOC bonds in these complexes may owe its origin to steric factors.

Although we have previously reported [1] weak complexes formed between organotin compounds and nucleic acid bases, none of these has proved suitable for X-ray diffraction. It is likely that in the presence of water the bases would be too weakly coordinating to give soluble species, as has recently been found for the reaction between $[SnMe_2Cl_2]$ and free purine in wet acetone [26]. In that study the purine moiety is found to be non coordinating at tin, even through the unblocked N_9 position of the purine. It therefore seems likely that the antitumour activity of organotin compounds must proceed by some fundamentally different mechanism from that of the platinum and related species, as there is no free hydroxyl group remaining on the sugar ring after formation of the DNA backbone where tin binding could take place. Tin could bind, for example to RNA or free nucleosides. Another line of evidence for a fundamentally different mechanism is the very different specificity found for the organotin compounds [9]. The platinum compounds are characteristically active against an extraordinary variety of tumours, whereas the tin compounds are mainly active against P388 lymphocytic leukemia.

Experimental

All the reagents were procured from commercial sources and used without further purification. The compounds were formed as water insoluble products when an aqueous solution of $[SnMe_2Cl_2]$ and corresponding nucleoside (1:2) (adjusted to pH 4–5 with HCl/NaOH) stirred at room temperature for between 1–24 h. White powdery products (>75%) were collected by filtration and washed thoroughly with hot water and finally with acetone and then dried.

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